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Citation

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Ain't Misbehavin'?
An Analysis of Prescription Drug Promotions by Pharmaceutical Manufacturers
and the Regulatory Response of the Food and Drug Administration (FDA)

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Class of 2003
March 2003

*This paper is submitted in satisfaction of both
the course requirement and the third year writ-
ten work requirement.*

Introduction/Abstract:

In evaluating the United States drug regulatory system in 1978, Richard J. Crout posed a choice between competing good values: “Do we want scientific rationality or personal freedom? And if we want the latter, are we willing to pay the price of a few frauds here and there?”¹ While the superiority of one policy preference over the other remains uncertain, since the answer largely depends upon the perspective of the “chooser” (i.e. consumer advocate or member/representative of the drug industry), what has become clear over the intervening twenty-five years is that Crout’s proposed tradeoff has materialized. Changes in the structure of the law including passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA), FDA’s 1997 draft guidance addressing advertisements through broadcast media (such as radio and television communications) incorporated under final regulations promulgated in 1999, recent trends in the courts’ First Amendment treatment of commercial speech concerning drugs, and the January 2002 Health and Human Services (HHS) policy requiring FDA legal review of regulatory letters before they are sent to drugmakers, all embody, either in theory or in practice, a loosening of the restrictions placed upon pharmaceutical manufacturers. At the same time, fraudulent promotional practices pervade the marketplace as manufacturers run deceptive ad campaigns marketing drugs as safer and/or more effective than they really are, obscuring and minimizing risks and/or failing to present information about adverse side effects, marketing unapproved uses for an approved drug, and commercializing experimental drugs that have not yet received NDA approval. This paper will explore the impact, if any, had by the changes in the legal landscape upon drugmakers’ marketing practices, raising the issues of whether certain unlawful practices may in fact be desirable, and whether the current level of FDA enforcement is appropriate to meet these practices.

Part I of this paper will address the extent of FDA’s jurisdiction to regulate promotional activities by or on behalf of prescription drug manufacturers and provide a historical background for why regulation of

prescription drug advertising is necessary. Part II will explore the rise of direct-to-consumer advertising and the prevalence of misleading promotional materials in the context of the relaxed FDA guidance regarding broadcast media and the HHS policy governing FDA regulatory letters. Part III will study advertising as tailored to physicians and the relationship between drug companies and doctors against the background of the FDAMA's provision on dissemination of information on off-label drug use. Part IV will examine the First Amendment constitutionality of restrictions on commercial speech concerning drugs in the wake of recent Supreme Court decisions and the Washington Legal Foundation cases. Part V will address manufacturers' promotion of unapproved drugs in relation to the pros and cons of speeding patients' access to new drugs. Lastly, Part VI will examine proposed recommendations for FDA enforcement measures.

I. Scope of FDA's Statutory Authority:

The first federal law regulating the advertising of drug products was established in 1914 with the creation of the Federal Trade Commission (FTC), to which Congress delegated the authority to regulate "unfair methods of competition in commerce," a mandate interpreted by the agency to include the prohibition of false and misleading advertisements.² Enactment of the Wheeler-Lea Act in 1938 specifically empowered the FTC to prevent the use of false or deceptive statements in advertisements of food, drugs, and cosmetics, but left a loophole for prescription drug advertisements disseminated solely to physicians and failed to provide the FTC with authority to compel an affirmative disclosure of information.³ Thus, pharmaceutical manufacturers were left without any check on their ability to present drug advertisements to physicians in a misleading manner, resulting in product claims that lacked balanced information and were either wholly

²Pyrich, Alissa and Walsh, Charles J. "FDA Regulation of Pharmaceutical Advertising: Symposium on the U.S. Pharmaceutical Industry in the 1990's: Facing Health Care Reform, Regulation and Judicial Controls." 24 SHLR 1325, 1335 (1994).

³*Id.* at 1336-7.

unsupported or supported by unreliable evidence. It was not until Congress enacted the 1962 Amendments to the Food Drug and Cosmetics Act of 1938 (FDCA), in reaction to the thalidomide tragedy in Europe, that efficacy requirements were added for approval of new drug applications and exclusive jurisdiction was transferred from the FTC to the FDA over prescription drug advertising.

Prior to these Amendments, the FDA expansively interpreted the authority it was given by the FDCA to regulate the labeling of prescription drug products. “Labeling” is defined by the FDCA to encompass “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying any such article.”⁴ As the Supreme Court held in *Kordel v. United States*, the second clause of § 321(m) is not limited to labels that are physically attached to the article, container, or wrapper that is transported, so that promotional materials which perform the function of supplementing or explaining the use of the product fall within the definition of labeling.⁵ If the labeling is “false or misleading in any particular” or fails to bear “adequate directions for use” or “adequate warnings” against dangerous uses, then the product is “deemed misbranded.”⁶

Under the FDCA of 1938, as amended, a drug product might also be deemed misbranded for failure to comply with the minimum content requirements for advertisements. Although not expressly defined within the FDCA, examples of “advertisements” subject to FDA regulation have been listed by the FDA to include “advertisements in published journals, magazines, other periodicals and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.”⁷ Affirmative disclosure rules were first promulgated by the FDA in 1963, but revised in the mid-1970s, so that the current regulations for advertisements of prescription drugs require: (1) a true statement of the established name

⁴21 U.S.C. § 321(m).

⁵*Kordel v. United States*, 335 U.S. 345 (1948).

⁶21 U.S.C. § 352(a) and (f).

⁷21 C.F.R. § 202.1(1)(1)(1993).

for the drug and its formula; and (2) a brief summary of information about the drug relating to its side effects, contraindications for its use, and its effectiveness.⁸ Advertisements must be fairly balanced so that any negative or cautionary information is presented in comparable depth and detail as any claims about the effectiveness and safety of the drug.⁹ Moreover, pharmaceutical manufacturers are specifically prohibited from promoting any unapproved use for an approved drug.¹⁰

Aside from a misbranding charge covering a violation of either the labeling or advertising provisions of the FDCA, a third possible source of FDA statutory authority to regulate drug industry marketing activities might be seen to stem from the FDCA prohibition against introduction into interstate commerce of any unapproved new drug.¹¹

The logic of the unapproved new drug argument follows from the idea that the FDA views statements about the intended use of a product as capable of turning an approved new drug into an unapproved new drug. However, the flaw in this logic rests with the conflation of the two concepts of “drug” and “new drug.” The phrase “intended use” comes from the definition of a “drug”: “articles intended for use in the diagnosis, cure, mitigation, or prevention of disease;”¹² whereas a “new drug” refers to any drug not generally recognized as safe and effective “for use under the conditions prescribed, recommended, or suggested *in the labeling thereof*.”¹³ Thus, materials that do not constitute labeling cannot transform a “drug” into a “new drug,” thereby limiting FDA’s new drug authority. FDA can still bring a misbranding charge, though, based on non-labeling information that suggests an intended use for which the drug’s label fails to bear adequate

⁸21 U.S.C. § 352(n).

⁹*Supra* note 2 at 1346.

¹⁰21 C.F.R. § 202.1(e)(4)(i)(a), (ii) & (iii); *id.* § 202.1(e)(6)(i).

¹¹Boulding, Mark E. “The Statutory Basis for FDA Regulation of Scientific and Educational Information.” 4 J. Pharmacy & L. 123, 128-9 (1995).

¹²21 U.S.C. § 321(g)(1).

¹³21 U.S.C. § 321(p)(1) (*emphasis added*).

directions.¹⁴

Even once the statutory authority for FDA regulation has been located, it is still important to ask why government regulation of prescription drug advertising is at all necessary? If advertising regulation is primarily aimed at protecting consumers from false, misleading, or deceptive product claims in terms of preserving consumers' economic and health related expectations, won't the economic self-interest of manufacturers, in turn, prompt most advertisers to avoid false or misleading claims or to correct inaccuracies before consumer confidence is undermined in the product? The problem with leaving advertising to market self-regulation in the case of prescription drugs is that these products, termed "credence goods," possess qualities that cannot be assessed by the consumer through normal use.¹⁵ Thus, even experienced health care professionals depend upon pharmaceutical manufacturers to provide accurate and reliable information about how and when to use their products. Moreover, taking into account the potential side effects of death or serious injury from false or misleading information about drug products, the need for governmental regulation of prescription drug advertising becomes readily apparent.

II. Direct-to-Consumer Advertising and Misleading Messages:

Serving the twin policy goals of "providing consumers with adequate communication of the required risk information," while facilitating the process used by advertisers to market their products to consumers, the FDA issued a non-binding proposed guidance in 1997 to relax the "brief summary" requirement for radio and television advertisements.¹⁶ Formerly, only "help-seeking" and "reminder" advertisements were exempt from having to contain a brief summary describing the drug's side effects, contraindications, warnings,

¹⁴*Supra* note 11 at 138.

¹⁵*Supra* note 2 at 1330-1.

¹⁶Draft Guidance for Industry; Consumer-Direct Broadcast Advertisements, 62 Fed. Reg. 43, 172 (1997).

and indications for use.¹⁷ While print media could easily comply with the brief summary requirement by reproducing the text of the package insert in the advertisement, broadcast advertisers were subject to special constraints. Under the current FDA regulatory guidelines promulgated in 1999,¹⁸ an “adequate provision” requirement was implemented to modify the brief summary standard for radio and television advertising, so that drug manufacturers may simply identify the product’s major risks in lay language during the broadcast, as long as the manufacturer provides for the delivery of approved package labeling in connection with the broadcast presentation.¹⁹

What if any impact did the relaxed regulatory guidelines for broadcast media have upon direct-to-consumer (DTC) advertising? A study by the Kaiser Family Foundation suggests that increases in DTC spending on television advertising were rapid even before the FDA draft guidance in 1997, so that the “adequate provision” rules could be seen as a response to shifts in promotional activity that had already occurred, as opposed to fueling the entire growth in DTC ads.²⁰ Still, health care experts cite DTC advertising as a leading cause of soaring prescription drug costs, with DTC spending having tripled to \$2.7 billion worth a year, roughly two-thirds on television and radio, since the FDA loosened drug promotion rules in 1997.²¹ Prescription drug costs, driven largely by higher utilization and also by higher pharmacy prices needed to recoup the huge expense of drug ads, increased nineteen percent in 2000 and another seventeen percent in

¹⁷Ausness, Richard C. “Will More Aggressive Marketing Practices Lead to Greater Tort Liability for Prescription Drug Manufacturers?” 37 Wake Forest L. Rev. 97, 102 (2002):

“Rogaine advertisements, which suggested that products were available to prevent hair loss but did not identify any of these products by name, exemplified the help-seeking variety of advertisement. The ‘blue skies’ Claritin advertisements of the early 1990s, which mentioned the product by name but failed to mention its medicinal purpose, exemplified the reminder type of advertisement.”

¹⁸See FDA, Guidance for Industry: Consumer-Directed Broadcast Advertisements (Aug. 1999). Available at: <http://www.fda.gov/cder/guidance/index.htm>.

¹⁹*Supra* note 17 at 103:

The sponsor can disseminate the contents of the approved package label to consumers by: (1) providing a toll-free telephone number where such information can be requested; (2) referring in the broadcast advertisement to a print advertisement or brochures available to the public which contain such information; (3) advising listeners or viewers to ask a pharmacist or doctor for further information about the product; and (4) providing an Internet web site where such information can be obtained.

²⁰Frank, Richard, Ph.D. et al. “Trends in Direct-to-Consumer Advertising of Prescription Drugs.” The Henry J. Kaiser Family Foundation. (Feb. 2002). Available at: www.kff.org.

²¹“Misleading Drug Ads Slip Under Regulators’ Radar.” *USA Today*, Jan. 6, 2003.

2001, with almost half of the increase in 2000 being driven by sales of the fifty most heavily advertised drugs.²² The Kaiser study found that high DTC spending generally appears to be associated with new products that have no generic competitors, although in some cases, manufacturers of products nearing the end of patent protection advertise directly to consumers because they need to build brand equity for the switch to over-the-counter status.²³ Spending on DTC advertising is concentrated among a relatively small number of products, particularly drugs used to treat chronic conditions like allergies, high cholesterol, and ulcers.²⁴ Moreover, many of the heavily advertised new drugs are simply “me too” medicines – basically the same as previously approved drugs whose patent expired about the same time the new drug was released.²⁵ Promoting costly new drugs without proportionately improving benefits puts pressure on corporate insurance plans and public programs which leads to reduced access, fewer benefits, and higher co-payments.²⁶

An implicit assumption underlying the FDA’s special accommodation of DTC advertising is that this method of marketing is beneficial – but for whom aside from pharmaceutical manufacturers? According to FDA’s January 2003 release of preliminary results from a survey asking 500 physicians about DTC prescription drug advertising, doctors cited positive public health benefits such as increased patient awareness of diseases that can be treated and more thoughtful questions raised during the doctor visit.²⁷ Dr. Martin S. Lipsky, professor and chair of family medicine at Northwestern University’s Feinberg School of Medicine, commented that, “In addition to calling attention to undertreated disorders, drug ads may make people more accepting of necessary treatments.”²⁸ Jeff Trewhitt of the industry’s Pharmaceutical Research and Manufacturers of America (PhRMA) noted that “direct-to-consumer advertising may also prompt improved compliance with

²²“Free reign for drug ads?” *Consumer Reports* (Feb. 2003), p.36.

²³*Supra* note 20.

²⁴*Id.*

²⁵*Supra* note 22.

²⁶Landauer, Robert. Editorial: “Oregon Seeks Drug-Hype Antidotes.” *Portland Oregonian* (April 2002).

²⁷FDA Talk Paper: “FDA Releases Preliminary Results of Physician Survey on Direct-to-Consumer Prescription Drug Advertisements.” (Jan. 2003) *Available at*: <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01189.html>.

²⁸*Supra* note 22 at 34.

medical treatments, which are cost-effective compared to the costs of surgery and hospitalization.”²⁹

Nonetheless, the FDA survey results are not unequivocally beneficial for consumers: fifty-nine percent of physicians said having seen a drug commercial added no benefit to a patient’s subsequent doctor visit; eight percent of doctors said they felt very pressured to prescribe the specific brand name drug the patient wanted, regardless of whether a different drug was more appropriate or a less expensive drug was available; about seventy-five percent of physicians believed that DTC advertising causes patients to think the drug works better than it really does; and only forty percent of physicians believed that patients understand very well or somewhat well the risks and negative effects of an advertised drug from the DTC ad alone.³⁰ It is important to note, though, that eighty-two percent of physicians believed that patients understand either very well or somewhat well that “only a doctor can decide if the drug is right for the patient.”³¹ This high percentage fits with the results of a recent patient survey by the National Consumers League which found that many patients use drug ads only as starting points for more information because they realize the ads are trying to sell drugs.³²

The positive public health benefits discussed earlier, though, rest on a second implicit assumption behind the FDA’s authorization of direct-to-consumer advertising: namely, that drug makers are telling the truth about what they’re marketing. However, lifting the restrictions on television and radio advertisements has opened the door to misleading ads that create unrealistic expectations and/or dismiss potential adverse side effects. In 1998, one year after the FDA allowed companies to advertise prescription drugs directly to consumers, the agency issued 157 warnings about deceptive ads.³³ *Consumer Reports* magazine conducted a computer-

²⁹*Id.* at 36.

³⁰*Supra* note 27.

³¹*Id.*

³²The Associated Press. “Many Physicians Say Ads Don’t Benefit Patients.” *Newday*, Jan. 21, 2003.

³³*Supra* note 21.

assisted analysis of 564 letters to prescription drugmakers posted on the FDA's web site from January 1997 through November 2002 to determine the nature and scope of false or misleading drug promotions.³⁴ "Omitting, minimizing, or obscuring a drug's risks" was the most common transgression, with 363 citations, followed by "inadequate or incorrect labeling information" at 230 citations, "misleading comparative or superiority claims" at 214 citations, and "false or unsubstantiated efficacy claims" at 203 citations.³⁵

Specific examples of misleading promotional activities by pharmaceutical manufacturers help bring these transgressions to light. Pfizer, maker of the cholesterol drug Lipitor, has been cited four times in four years for ads giving the wrong impression that it can reduce heart disease and falsely claiming Lipitor is safer than competing drugs.³⁶ Pfizer was again implicated in January 2003, this time for a \$6-million settlement with nineteen states that accused the company of misrepresenting the performance of Zithromax (an antibiotic used to treat severe ear infections in children), by focusing on fewer doses per day and fewer days needed for medication compared with competitors, and also failing to disclose the various factors that physicians take into account when prescribing a treatment for ear infections.³⁷ Also in January 2003, makers of the painkiller Oxycontin were warned by the FDA to immediately cease running print ads for the drug which "grossly overstate the safety profile of OxyContin by not referring in the body of the advertisements to serious, potentially fatal risks associated with the drug."³⁸ The year before, the FDA reprimanded four drugmakers for misleading promotions in the month of January: AstraZeneca for its Nolvadex advertisements (a breast cancer drug) which failed to point out that the drug may increase a patient's risk of developing uterine cancer; ICN Pharmaceuticals Inc. for its advertisements for Efudex (used to treat pre-cancerous lesions)

³⁴*Supra* note 22 at 35.

³⁵*Id.*

³⁶*Supra* note 21.

³⁷The Associated Press. "Pfizer to Pay States \$6M." *Newsday*, Jan. 7, 2003.

³⁸Adams, Chris. "FDA Asks Maker of OxyContin to Pull 'Misleading' Print Ads." *The Wall Street Journal*, Jan. 23, 2003: Note: Purdue Pharma LP ran the OxyContin ads in the Journal of the American Medical Association (JAMA) and claimed the ads were aimed at doctors, not the general public.

which downplayed risks such as the potential for miscarriage when applied during pregnancy; Pharmacia Corp. for claims about the drug Genotropin (used to treat stunted growth) which confused readers by failing to denote the drug's approval only for children up to age two; and Abbott Laboratories for distributing promotional materials about the Meridia obesity drug that overstated the drug's efficacy.³⁹ Perhaps even more controversial is the claim that pharmaceutical companies have created a new disorder of female sexual dysfunction to build a market for Viagra and similar drugs among women by wrongly "medicalizing" female sexual problems and greatly exaggerating the number of women affected.⁴⁰ While drugmakers say knowledge of the condition pre-dated Viagra and they are simply seeking a treatment option for millions of women with sexual difficulties, author of the British Medical Journal article disclosing the allegedly corporate sponsored creation of the disease argued that the figures cited by the industry for female sexual dysfunction were misleading and potentially dangerous.⁴¹

FDA Enforcement Response:

Ironically, as the need for even stricter FDA oversight is made clear by the increase in spending on direct-to-consumer advertising and the proliferation of misleading messages that are thereby reaching consumers, the regulatory process has instead been dramatically slowed by a Bush administration policy change. Typically, promotions for new prescription drugs must be submitted to the FDA when they're first used, but drug companies can run the ads without pre-approval, subject to post-market enforcement by the FDA in the form of a "notice of violation" or "warning letter."⁴² If a company ignores a warning letter sent by the FDA,

³⁹Bloomberg News. "FDA Reprimands 4 Drug Makers for Misleading Promotions." *Los Angeles Times*, Jan. 16, 2002.

⁴⁰Reuters. "Article: Sex Disorder Made Up." *Newsday*, Jan 4, 2003. See also "Female impotence: Firms under fire" and "Study suggests women's sex problems may be less than thought" both available at: <http://www.cnn.com/2003/Health/conditions/>

⁴¹*Id.*

⁴²*But see* FDA non-binding guidance on pre-approval promotion: Hayes, Thomas A., M.D. "Drug Labeling and Promotion: Evolution and Application of Regulatory Policy." 51 Food & Drug L.J. 57, 67 (1996): The guidance lists two basic forms of

the agency can then take the company to court to enforce compliance. Following the Bush administration procedure implemented in January 2002, the Department of Health and Human Services (HHS) began requiring legal review of all proposed regulatory letters about drug ads *before* they are mailed to the offending company.⁴³ According to HHS officials, the purpose behind this extra step is to ensure that the FDA can back up its claims about misleading ads if challenged in court. However, an investigative report made public by the General Accounting Office (GAO) in December 2002 found that the new procedure has held up FDA letters from two to eleven weeks.⁴⁴ From 1997 to 2002, the FDA sent eighty-eight letters to companies citing inaccurate advertising claims about a drug's safety or efficacy, and the companies stopped running the misleading ads in all cases. In contrast, evaluating a letter now takes up to seventy-eight days.⁴⁵ According to Dr. Sidney Wolfe of the Public Citizen consumer advocacy group, by mid-December of 2002, the FDA had issued only twenty-seven letters ordering drug companies to stop a misleading ad, down from a high of 157 in 1998.⁴⁶ Congressional investigators announced that misleading advertisements "often had run through their schedules and gone off the air by the time the agency got around to chastising their makers."⁴⁷ Thus, review of letters intended to warn drugmakers that the FDA is prepared to take legal action if the companies don't comply with advertising regulations essentially undercuts that aim by signaling to the drug industry that "intensive, quick-hit promotional campaigns are effectively immune from sanction."⁴⁸

In defense of the pharmaceutical industry, Bruce Kuhlik, a lawyer for PhRMA, said "the fact that the announcement that are acceptable. The first uses the product name and the second, known as the "institutional" or "corporate" format, identifies only the area of research involved in developing the new product. Restrictions on pre-approval promotion vary depending on the format employed.

⁴³*Supra* note 22 at 34.

⁴⁴*Id.*

⁴⁵"FDA Seeks Rx for Drug Ads / New policy delays process." *Newsday*, Dec. 5, 2002.

⁴⁶The Associated Press. "New Commissioner of FDA Pledges to Fight Misleading Drug Ads: But Agency has Issued Fewer Warning Letters, Consumer Advocate Says." *St. Louis Post-Dispatch*, Dec. 12, 2002.

⁴⁷*Id.*

⁴⁸*Supra* note 21.

number of requests to end misleading ads has dropped indicates that the industry is doing a better job at complying with the law.”⁴⁹ Meanwhile, industry representatives focus on the GAO’s report showing that far more dollars are spent on research and development of drugs than on promotions.⁵⁰ Yet, as Representative Henry Waxman, of California, pointed out, “The precipitous drop in enforcement actions may be a welcome development for the drug industry, but it poses serious dangers to public health.”⁵¹ His sentiment is echoed by consumer advocates like Wolfe from Public Citizen who noted the “chilling effect” of the policy change on the regulatory process and commented that misleading advertisements, “can make the difference between someone getting the right drug and the wrong drug; it’s a health and safety issue.”⁵² FDA’s commissioner, Mark McClellan, and inspector general at HHS, Janet Rehnquist, both promised faster action and set a goal for the agency to issue enforcement letters within fifteen working days. However, the resource constraints faced by the FDA in terms of staffing shortages⁵³ and the inability to levy fines upon drug companies, coupled with the fact that ad campaigns may still be able to run their course even within the shorter turnover time, place administrative and practical obstacles in the path of FDA’s ability to meet this goal.

Politics of a well-connected industry?

Just as the HHS executive policy requiring FDA legal review signals lax enforcement to the pharmaceutical industry – “which has given more than \$45 in campaign contributions since 1999”⁵⁴ – politics may also play a role in changing the regulatory terrain through the courts, as demonstrated by the result of the class-action lawsuit brought by thirty-five patients suffering withdrawal symptoms from the anti-depressant drug Paxil.⁵⁵

⁴⁹Powell, Jennifer Heldt. “FDA spanked on policing of drug ads.” *Boston Herald*, Dec. 5, 2002.

⁵⁰*Id.*

⁵¹*Supra* note 22 at 34.

⁵²*Supra* note 46.

⁵³“The office, responsible for evaluating all direct-to-consumer drug advertising, currently employs just five people, with two slots vacant.” *Supra* note 45. *See also supra* note 22: “The agency has only about 30 reviewers to handle the roughly 30,000 submissions each year.”

⁵⁴*Supra* note 21.

⁵⁵Lota, Louinn. “Paxil’s maker ordered to pull ‘misleading’ ads.” *The Milwaukee Journal Sentinel*, Aug. 21, 2002.

Daniel E. Troy, chief legal counsel of the FDA since August 2001, championed the causes of pharmaceutical companies against the FDA for years prior to joining the agency. Even after assuming the role of chief counsel, Troy filed a brief in defense of GlaxoSmithKline in the Paxil case, aligning the FDA's position with that of the industry by saying "the FDA agrees with the allegation that Paxil is not a habit-forming drug."⁵⁶ The characteristic of "habit-forming" turned on the distinction between "withdrawal symptoms" versus "discontinuation syndrome," but the underlying question remained "whether patients, lacking medical or legal education, could be expected to know the scientific difference between those phrases."⁵⁷ U.S. District Judge Mariana Pfaelzer answered this question in the negative, holding the ads to be misleading and ordering the maker of Paxil to halt all television commercials nationwide that claim the drug is not habit-forming.⁵⁸ The judge ended up lifting her temporary order, however, in response to Troy's argument that the FDA has the ultimate authority to decide the question, and had already reviewed the precise ad prior to use without raising any objections to the language at issue.⁵⁹ Troy's position may be seen as hypocritical, though, as one of the plaintiff attorneys in another anti-depressant drug case points out: "Dan Troy basically built his career representing pharmaceutical companies suing the FDA, arguing that FDA determinations are arbitrary and capricious... [now] he has been issuing this mantra that the court cannot review the FDA's factual determination."⁶⁰ Pfaelzer herself wrote, "It is difficult to imagine that the FDA would object to the removal of the reference that 'Paxil is not habit-forming.'"⁶¹

In this way, the role of politics combines with the issue of limited resources to pose both internal and external constraints upon the FDA, weakening its stance against the pharmaceutical industry and hampering its ability to halt misleading DTC promotions.

⁵⁶Kranish, Michael. "FDA Counsel's Rise Embodies U.S. Shift." *The Boston Globe*, Dec. 22, 2002.

⁵⁷*Id.*

⁵⁸*Supra* note 55.

⁵⁹*Supra* note 56.

⁶⁰*Id.*

⁶¹*Id.*

III. Drug Promotions to Physicians and the Impact of the FDAMA:

Despite the disproportionate growth in DTC ads relative to other forms of drug promotion over the last decade, physicians remain the primary focus of marketing efforts, including both office-based and hospital based physician promotion, the retail value of free samples, and advertising in medical journals.⁶² Moreover, from January 1997 through November 2002, doctors and others who prescribe medicines were exposed to nearly four times as many messages deemed false or misleading by the FDA as were consumers.⁶³ The tension between scientific rationality and personal freedom surfaces here with respect to the regulatory treatment of one such type of misinformation provided to doctors – promotion of approved drugs for unapproved purposes, referred to as “off-label” indications.

The term “off-label” comes by inference from FDA drug product labeling requirements. Pharmaceutical companies are required to convey, in the drug’s formal labeling, information necessary for safe and effective use of the product (i.e. warnings, precautions, indications, contraindications, clinical pharmacology, adverse reactions, etc.) for those particular uses for which the drug was approved. All other uses are designated as “off-label,” encompassing “use by persons other than those for whom the drug was approved, use in dosages other than the approved dosages, use for conditions other than those indicated in the labeling, and use in unapproved combination with other drugs.”⁶⁴ Off-label prescription of drugs, like off-label use itself, is not per se unlawful. A physician may, as part of the practice of medicine, vary the conditions of use for a prescription drug from those approved in the package insert without first informing or obtaining the consent of

⁶²*Supra* note 20.

⁶³*Supra* note 22.

⁶⁴Salbu, Steven R. “Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy.” 51 Fla. L. Rev. 181, 188 (1999).

the FDA.⁶⁵ Similarly, the manner in which a drug is used lies within the independent control of the patient once the prescription drug is in his/her hands. However, as discussed above under Part I, FDA’s regulation of product labeling authorizes the agency to prevent manufacturers from distributing promotional materials advocating off-label uses of approved drugs. The rationale behind this prohibition, to protect the public health from harmful off-label uses and ensure complete and accurate information regarding the use and risk of drugs, ties into the rationale behind the new drug approval (NDA) process.

With the “efficacy” requirements added to the safety provisions of the NDA process in 1962, Congress specified the “substantial evidence”⁶⁶ standard for clinical data that a manufacturer must submit for *each intended use* of the drug. Information regarding unapproved uses correspondingly lacks the guarantee of pre-clinical and Phase I, II and III scientific support for those uses, thus giving rise to the FDA’s general unwillingness to allow promotion of such uses. If a pharmaceutical manufacturer wishes an off-label use to be added to the drug’s labeling, the manufacturer must submit new reports of clinical trials regarding the new use. The results of the Phase I study (showing overall safety and absence of adverse effects) that was already conducted for the approved drug would probably be sufficient, however new Phase II and Phase III trials – the most expensive part of the new drug approval process – would still be required to demonstrate the efficacy of the new use.⁶⁷ Moreover, the median approval time for standard drug applications increased in 2002 to 15.3 months, up from 14 months in 2001 and 12 months in 2000.⁶⁸ Thus, the tediousness and expensiveness of FDA procedures coupled with the fact that inclusion of a new use in the drug’s labeling may not even increase the drug’s sales (considering that off-label applications might already be well known

⁶⁵“Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rulemaking.” 37 Fed. Reg. 16503 (Aug. 15, 1972).

⁶⁶The 1962 Drug Amendments defined “substantial evidence” as:

“evidence consisting of adequate and well-controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.” 21 U.S.C. § 355(d).

⁶⁷Weeks, Elizabeth A. “Is it Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use Under the Food and Drug Administration Modernization Act of 1997.” 54 Food and Drug L.J. 645, 655 (1999).

⁶⁸“FDA Capsules: Drug Approval Times.” *Newsday*, Jan. 21, 2003.

and in widespread use), explain pharmaceutical manufacturers' disincentive to seek permission to market off-label uses of their products.

The FDA's own regulations are actually difficult to reconcile with the question of whether restrictions on the dissemination of off-label information should be upheld. While Section 202.1(e)(4) of the agency's advertising regulations provide that manufacturers cannot recommend or suggest any use that is not in the labeling in an approved NDA, Section 312.7(a) of the investigational new drug (IND) regulations qualify the prohibition on representing an investigational drug as safe and effective "in a promotional context" by encouraging the "full exchange of scientific information concerning the drug."⁶⁹ While the latter statement comes from a section dealing with investigational drugs as opposed to approved, marketed drugs, the same policy of encouraging scientific dialogue and innovation by giving manufacturers more personal freedom can be applied to the promotion of off-label uses for approved drugs. Kenneth R. Feather, acting director of the FDA Division of Drug Advertising and Labeling in 1989, raised the countervailing policy point of scientific rationality in a speech during the annual meeting of the PMA Marketing Section: "If most of these [off-label] uses are not going to be adequately studied and proven, how can this information help a physician use the drug 'properly'? . . . Doesn't this look more like a way to make sure the drug is used for all of these problems, without the company having to do the studies to properly prove them?"⁷⁰ In answering the threshold question of how to identify what constitutes prohibited off-label marketing in contrast to permissible scientific exchange – attempting to strike the appropriate balance between access to information and protection of the general welfare – the FDA and Congress developed a regulatory approach in the 1990s designed to liberalize the dissemination of information regarding off-label uses. Whether the rules operate in practice to achieve that result and whether the intended result would even be desirable if achieved is subject to debate.

The "gray area" for the distinction between promotion and education arises when, for example, sponsors of

⁶⁹Hutt, Peter Barton and Merrill, Richard A. Food and Drug Law. Foundation Press, New York (1991). p.462

⁷⁰*Id.* at 463.

approved drugs distribute medical journal articles - written by parties unaffiliated with the industry sponsor - that discuss the results of clinical investigations of off-label uses of the drugs.⁷¹ The FDA issued a draft guidance in December 1995, followed by promulgation of a final guidance in October 1996, explaining the circumstances under which dissemination of off-label use reprints would be acceptable for pharmaceutical manufacturers. Any articles distributed must be “peer-reviewed, published descriptions of the original clinical studies assessing drug effectiveness ... and the principal subject of the article should be the use(s) or indication(s) approved by FDA.”⁷² Textbooks containing discussions of off-label uses are also permitted (maintaining the requirement that the principal subject pertain to approved uses) as long as the manufacturer did not influence the production of the text or request to serve as the book’s primary distributor.⁷³ Whether articles or textbooks, the package insert is the only acceptable form of information that may be attached to the materials distributed.⁷⁴

The FDA guidance, found unconstitutional in *Washington Legal Foundation (WLF) v. Friedman*,⁷⁵ was superceded in 1997 by Section 401 of the Food and Drug Administration Modernization Act (FDAMA), which added Sections 551-557 to the FDCA, establishing specific conditions under which drugmakers can lawfully disseminate off-label use materials.⁷⁶ The FDAMA allows for distribution of unabridged versions of qualified written information⁷⁷ concerning the safety, effectiveness, or benefit of off-label uses to the following enumerated groups: (1) health care practitioners, (2) pharmacy benefit managers, (3) health insurance issuers, (4) group health plans, and (5) federal or state government agencies.⁷⁸ Note that to qualify for the

⁷¹Ward, Shane M. “WLF and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration’s Regulation of Off-Label Drug Use Information on the Internet.” 56 Food & Drug L.J. 41, 46 (2001).

⁷²Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800 (1996).

⁷³*Id.*

⁷⁴*Id.*

⁷⁵13 F. Supp. 2d at 74. Note: the WLF cases will be discussed *infra* under Part IV of this paper.

⁷⁶*Supra* note 71 at 47.

⁷⁷Qualified written information refers to a:

(A) reprint or copy of an article, peer-reviewed by experts qualified by scientific training or expertise ... which was published in a scientific journal ... which is about a clinical investigation with respect to the drug ...; or
 (B) reference publication ... that includes information about a clinical investigation with respect to the drug that would be considered to be scientifically sound by experts qualified ...” *Id.*

⁷⁸*Id.* at 48.

FDAMA provisions, pharmaceutical manufacturers must have already filed a new drug application for the prescription drug.

Despite the apparent loosening of restrictions on manufacturers' ability to market off-label indications, administrative obstacles remain in place to counteract the freedom provided by the legislation such that critics of the FDAMA question whether any reform has in fact been made. The FDAMA mandates that the manufacturer submit the off-label materials to the FDA sixty days prior to distribution along with any available clinical data related to the safety and effectiveness of the new use.⁷⁹ Also prior to dissemination, the manufacturer must certify to FDA one of the following: a supplemental application for the new use has been submitted; a supplemental application will be submitted within six months of dissemination; acceptable clinical protocols for the studies have been submitted and the corresponding supplement will be filed within thirty-six months; or the product sponsor falls under one of two exemptions on the basis that submitting a supplemental application would be "economically prohibitive" or "unethical."⁸⁰ In addition to the supplemental application requirement, there is a disclosure requirement that eligible information must be objective and balanced (not false or misleading) and must be accompanied by "prominently displayed disclosures of the unapproved nature of the use, the financial interests of the party disseminating the information, and any relationship between the sponsor and the author, including possible sources of research bias."⁸¹ The information must also be accompanied by a bibliography listing references to other publications or journal articles concerning the particular drug.⁸² The FDAMA provides a final safeguard in the form of corrective action by the Secretary of HHS should he/she determine that the new use is "ineffective or significantly risky to public health," or that the manufacturer has failed to comply with the statutory requirements.⁸³ The FDA may then require the manufacturer to submit additional information and/or order the manufacturer to cease

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² *Supra* note 64 at 216.

⁸³ *Id.*

dissemination of the off-label materials altogether. In November 1998, the FDA promulgated implementing regulations for the FDAMA, giving substance to the terms “new use”⁸⁴ and “scientifically sound,”⁸⁵ as well as confirming that exceptions to the supplemental application requirement will be interpreted narrowly.⁸⁶

Would it be desirable to eliminate the supplemental restrictions and thereby enable the FDAMA to have more of a practical effect in freeing manufacturers to distribute off-label information? What is the appropriate level of regulatory control? The concern about scientific validity of industry research conducted outside of the NDA process, whether because the standards applied may be less rigorous or because the results may be biased when financed by for-profit companies, cuts in favor of maintaining restrictions on information dissemination for unapproved uses of approved drugs. Similarly, making off-label information more readily available may increase patient exposure to riskier treatment methods and pose serious health consequences. On the other hand, the lengthy NDA process may work to the detriment of patients by delaying their ability to obtain beneficial therapies; a physician might have been able to competently evaluate the needs and risks of his/her patient to arrive at a less conservative risk-benefit calculus in a shorter time frame.⁸⁷ As portrayed in a Letter to the Editor by the General Counsel of the Competitive Enterprise Institute in Washington, “Overcaution in evaluating new life-saving therapies can be as deadly as lack of caution. Doctors need more information about off-label use, not less. The real threat to public health isn’t from off-label research, but from attempts to restrict it.”⁸⁸ Just because scientific research is industry-sponsored does not necessarily mean the results lack validity, and doctors as “learned intermediaries” are in a better position than consumers to make this determination. Off-label uses can constitute the most effective treatment or

⁸⁴“New use” is defined broadly to include: “indications, dosing schedules, routes of administration, age groups and patient populations not identified explicitly in the labeling.” See 21 C.F.R. § 99.3(g); 63 Fed. Reg. at 64,559.

⁸⁵See *id.* § 99.101(a)(2); 63 Fed. Reg. at 64,583.

⁸⁶*Supra* note 71 at 49.

⁸⁷*Supra* note 67 at 658-9.

⁸⁸Kazman, Sam. Letter to the Editor: “Off-Label Drug Studies: Overcaution is Risky.” *The Wall Street Journal*. Jan. 14, 2002.

even be considered the standard of care,⁸⁹ particularly in the case of pediatric prescriptions since many drugs are not tested for use by children.⁹⁰ It is also important to factor resources into the analysis in so much as the costs of an absolute ban of off-label promotion by pharmaceutical manufacturers would cost less than a monitored dissemination scheme under the FDAMA. Moreover, off-label marketing might actually be a potential source of cost-containment in so much as subjecting all uses of a drug to FDA approval increases the number of clinical trials conducted, raises manufacturer research and development expenditures, and consequently passes costs on to consumers in the form of price increases.⁹¹ The possibility of alternative means to reduce the risks associated with off-label applications other than restrictions on the dissemination of information to physicians will be discussed under enforcement recommendations in Part VI of this paper.

Too Close for Comfort?

While the FDAMA permits drug companies to share research and journal articles that discuss unapproved uses for approved drugs, pharmaceutical manufacturers are still prohibited from suggesting to physicians that they incorporate those uses into their practices. However, Continuing Medical Education (CME) courses are not subject to this same restriction and may discuss unapproved uses of commercially available drugs, which doctors are then free to prescribe as they deem fit.⁹² Thus, through corporate-sponsorship of CME courses, there exists a “backdoor way” for companies to establish close relationships with doctors and more broadly promote off-label indications for their products – an advertising strategy which has intensified since the pharmaceutical industry adopted a new voluntary marketing code of conduct, effective July 1, 2002.⁹³

According to PhRMA President Alan F. Holmer, the code “explicitly spells out that all interactions should

⁸⁹*Id.* In chemotherapy, doctors might actually be guilty of malpractice for limiting their prescriptions to FDA-approved uses.

⁹⁰*Supra* note 64 at 193.

⁹¹*Id.* at 195.

⁹²Hensley, Scott. “Remedial Lessons: When Doctors Go to Class, Industry Often Foots the Bill.” *The Wall Street Journal*, Dec. 4, 2002.

⁹³*Id.*

be focused on informing healthcare professionals about products, providing scientific and educational information, and supporting medical research and education.”⁹⁴ The code goes on to state that “nothing should be offered [by industry] or provided in a manner or on conditions that would interfere with the independence of a health care professional’s prescribing practices.”⁹⁵ The tactical shift by manufacturers from bestowing lavish gifts upon doctors to paying for or offering more consulting opportunities, continuing medical education courses, and dinners billed as educational events with specialist speakers was occurring even before the industry announced the new guidelines in July. The money spent by pharmaceutical firms on meetings and events including CME classes, teleconferences, dinners, symposia and get-togethers with physician advisers more than doubled over four years to \$2.1 billion in 2001.⁹⁶ The question remains, then, whether this form of involvement fulfills the goals of the industry’s code to benefit patients and enhance the practice of medicine without exerting improper influence over physicians?

Drugmakers point to the benefits of continuing medical education classes in that they provide physicians with crucial information about medicines and medical advances that can help patients, while at the same time creating a forum at which doctors can communicate with each other about their experiences. Thirty-six states require doctors to take continuing education to maintain their medical licenses; in those states, the average requirement is about twenty-seven hours of lectures or seminars a year.⁹⁷ Jeffrey Lieberman, professor of psychiatry at the University of North Carolina and a paid speaker for a number of industry-sponsored CME courses commented that, “For academic medicine to not avail itself of the resources of the pharmaceutical industry and private sector would be foolish.” Universities and hospitals that formerly charged doctors registration fees to attend class now routinely take money from the drug industry since physicians have

⁹⁴“PhRMA Adopts New Marketing Code.” April 19, 2002. Available at: <http://www.phrma.org/mediaroom/press/releases/19.04.2002.390.cfm>

⁹⁵*Id.*

⁹⁶Kowalczyk, Liz. “Drug Firms and Doctors: The Offers Pour In.” *The Boston Globe*, Dec. 15, 2002.

⁹⁷*Supra* note 92.

grown accustomed to industry-subsidized education and resist paying even small amounts.⁹⁸

Nonetheless, a concern expressed by Dr. Marcia Angell, former editor of the *New England Journal of Medicine*, that drug companies will “simply disguise marketing as education, slanting presentations toward their own products and helping to increase health-care costs,”⁹⁹ mirrors the belief articulated by Kenneth R. Feather in 1989 that a pharmaceutical manufacturing firm should not be able to “disseminate any information it wishes simply because they disguise it as a seminar or call it ‘education.’”¹⁰⁰ The inherent bias and conflict of interest that arises when companies offer education about a product they’re trying to sell undermines the drug companies’ professed goal of disseminating scientific information in an objective and non-promotional manner. The lack of enforcement provisions within the drug-industry code of ethics and the lack of FDA enforcement of its own regulations designed to prevent companies from using the educational system as a marketing device confounds this problem. The FDA’s main criteria for CME courses require that they be accredited and that drug companies not control course preparation, delivery, or content.¹⁰¹ Yet, drug companies remain free to suggest speakers as long as the education provider has the final approval, and some medical educators say that with corporate industry in control of the agenda, “doctors end up hearing a lot more about medical conditions that can be treated with expensive brand-name drugs and less about subjects from which manufacturers can’t profit.”¹⁰²

Post-marketing studies conducted for already-approved drugs tie into drug companies’ “backdoor” promotion of off-label indications at company-sponsored educational gatherings. For example, the marketers of Aricept, an Alzheimer drug approved only for mild to moderate stages of the disease, outlined the results of post-

⁹⁸ *Id.*

⁹⁹ *Supra* note 96.

¹⁰⁰ *Supra* note 70.

¹⁰¹ *Supra* note 92.

¹⁰² *Id.*

marketing studies to doctors at a January 2001 conference in Florida showing that the drug could help Alzheimer's even at late stages of the disease.¹⁰³ While the FDA doesn't allow drug company salespeople to mention post-market study results if unsolicited by the doctors to whom the information is being presented, psychiatrists claim that Aricept sales representatives are "definitely pushing the fact" that the drug can be of assistance regardless of the severity of the disease.¹⁰⁴ The rationale behind restricting the availability of off-label use information re-surfaces here in so much as post-marketing studies enable firms to skirt the NDA process with studies that might not pass muster with the FDA. Yet, the marketers of Aricept denied any efforts to bypass the NDA process, maintaining that their presentation of the studies has been "faithful to the data."¹⁰⁵ Moreover, the benefits of off-label use must not be ignored as post-marketing studies are necessary to learn more about how a particular drug works if medical improvements are to be made for progressive, largely untreatable diseases.

In evaluating the desirability and efficacy of regulatory action governing drug makers' promotion of off-label uses for approved drugs, it is important to trace the analysis back one step prior and consider whether there exist possible pharmaceutical marketplace incentives to avoid abuse. Theoretically, the reputational interest of drug companies in preserving consumer confidence in their statements should work not only to encourage self-regulation of fraudulent behavior, but also to encourage drug makers to monitor the educational programs sponsored by their competitors and report any promotional violations to the FDA.¹⁰⁶ Even absent the threat of FDA enforcement, market forces such as tort liability remain in place to discourage over-promotion by pharmaceutical companies and deter physicians from prescribing off-label drugs or therapies without reliable scientific support demonstrating safety and effectiveness.¹⁰⁷ While physicians won't be held liable for

¹⁰³Davis, Ann. "Data Points: Tactic of Drug Makers is Raising Questions About Use of Research." *The Wall Street Journal*, Jan. 7, 2002.

¹⁰⁴*Id.*

¹⁰⁵*Id.*

¹⁰⁶*Supra* note 2 at 1361.

¹⁰⁷*Id.*

prescribing a drug for unapproved uses that comport with currently accepted medical practice in the relevant community, doctors will otherwise be held responsible for deviations from approved uses as represented by the drug label or package insert. Health insurance policies reinforce compliance as unproven or experimental treatments are not reimbursed by most medical insurance plans.¹⁰⁸ However, a disconnect arises between theory and practice, whereby lax government enforcement leaves room for serious fraud, brought to the forefront by the current whistle-blower lawsuit pending in federal court in Boston, Massachusetts regarding the promotion of unapproved uses of the epilepsy drug, Neurontin.

Neurontin: A Case Study:

David Franklin, former employee of Warner-Lambert (which later became Parke-Davis and was acquired by Pfizer Inc. in 2000), claims the drug company forced employee participation in a national marketing scheme designed to illegally promote Neurontin for off-label uses (ranging from psychiatric disorders to migraines) by making exaggerated or false claims of safety and efficacy, bribing doctors with grants and consulting fees, and signing off on speakers hand-picked by the industry for continuing medical education courses, supposedly prepared by independent education providers.¹⁰⁹ The U.S. attorney's office in Boston, forty-seven states and the District of Columbia are investigating the allegations begun in 1996 that Warner-Lambert's promotion of the off-label benefits of the drug for uses that aren't Medicaid-eligible knowingly led doctors to write inappropriate prescriptions through at least 1998, violating the anti-kickback rules of the federally funded program.¹¹⁰ In Massachusetts, Neurontin is the fifth most costly drug for the state Medicaid program,

¹⁰⁸ *Id.*

¹⁰⁹ *Supra* note 92.

¹¹⁰ Chesto, Jon. "Suit questions off-label sales of Neurontin." *Boston Herald*, May 18, 2002.

which spent \$21 million on Neurontin last year; sales of the drug nationally, eighty percent of which are for unapproved uses, are expected to have exceeded \$2 billion in 2002.¹¹¹ The federal government has joined the suit as a co-plaintiff, seeking repayment for government outlays that were made to cover unapproved-use prescriptions.¹¹²

Four internal company memorandums from 1995, unsealed in federal court in early November 2002, outline Parke-Davis' estimated profit of \$150 million from the strategy of promoting Neurontin to doctors for bipolar disorder, social phobias, panic disorder, and neuropathic pain in journals and at medical conferences, without first seeking FDA approval for the off-label uses.¹¹³ The drug company's reasoning stemmed from a desire to leave more time for marketing the drug before expiration of the patent in 2000, when generics would then takeover the market. A "publication strategy" could be accomplished much more quickly than the investment in clinical trials that would be required to complete the NDA process and secure FDA approval. As part of this plan to publish studies, Parke-Davis contracted with a Philadelphia firm, Medical Education Systems, Inc., for an "educational grant" to develop a "scientific article series in support of epilepsy."¹¹⁴ However, the proposed articles focused mainly on off-label uses for the drug and Parke-Davis was given the unfettered right to "select the authors of the articles, receive pre-publication copies of the articles, and suggest changes to them."¹¹⁵ In a report entitled "1998 Neurontin Tactics," a New York City medical advertising firm hired by Parke-Davis outlined various strategies for promoting off-label use, including bipolar CME, even though psychiatrists said the drug had never been proven effective for these purposes.¹¹⁶

¹¹¹Kowalczyk, Liz. "Drug Firm Seen Skirting FDA OK: Unapproved Uses Promoted for Profit." *The Boston Globe*, Nov. 2, 2002.

¹¹²*Supra* note 92.

¹¹³*Supra* note 111.

¹¹⁴Armstrong, David and Forelle, Charles. "Health & Technology: Drug Officials May Have Broken Rules on Neurontin." *The Wall Street Journal*, Dec. 20, 2002.

¹¹⁵*Id.*

¹¹⁶Kowalczyk, Liz. "Neurontin Marketing Plan Disclosed: Drug Maker Hired 3 Firms to Promote Unapproved Uses." *The Boston Globe*, Nov. 8, 2002.

Franklin's attorney, Thomas Greene, responded to the pharmaceutical manufacturer's advertising strategy by posing the question, "If we're going to permit a drug company to get narrow approval and then allow them to market the drug for a whole bunch of unapproved uses, why even have an FDA? How are we going to protect the public?"¹¹⁷ The obvious danger of permitting drug companies to bypass the rules lies in the flow of untrustworthy information to doctors and the corresponding impact on inappropriate prescriptions. The case of Dustin Yankus, a 16-year-old boy who suffered from bipolar disorder and committed suicide in May 2002, raises the question of why doctors turned to Neurontin to treat Dustin's disorder despite his complaints during the previous eight months that the drug wasn't working.¹¹⁸ While Dr. Catherine Clarey, senior medical director at Pfizer, says there is "absolutely no evidence" that Neurontin can cause suicidal behavior, this does not alleviate the concern about indirect harm presented by the failure to prescribe more effective medication or seek alternative treatment.¹¹⁹

Neurontin is not the only drug for which off-label promotion has become a recent issue. A consumer group filed suit in California Superior Court on December 23, 2002, claiming that Pharmacia Corp. is illegally promoting use of the drug Bextra for acute pain caused by impacted molars.¹²⁰ Bextra is FDA-approved only for chronic pain associated with arthritis, osteoporosis, and menstrual cramps. The lawsuit alleges that the drug company "went against the spirit of the law" by conducting the study aimed at this off-label use when the FDA specifically refused to approve the company's request for an indication for acute pain.¹²¹ Whether the attempt to seek FDA permission should cut for or against the drug company promoting off-label uses is debatable, though, as the Neurontin case demonstrates a surreptitious approach to avoid the FDA approval

¹¹⁷*Supra* note 111.

¹¹⁸NPR Programming. "The Selling of Neurontin." Jan. 16, 2003. *Available at:* <http://www.npr.org>.

¹¹⁹*Id.*

¹²⁰Associated Press. "California Suit Claims Pharmacia Skirts Marketing Rules." *Los Angeles Times*, Dec. 26, 2002.

¹²¹*Id.*

process altogether. Similarly, the FDA cited Allergan, Inc., the maker of Botox Cosmetic wrinkle injections, for promoting the product for unapproved uses within its drug ads, discussing different dosing schedules that could confuse the physician and suggesting the product is intended to treat signs of aging, when in fact Botox has only been approved for temporary and limited use for cosmetic purposes.¹²² Allergan actually refused to pull the drug ads as requested, opting to draft an official response to the agency at which point the FDA will decide what, if any, action should be taken.¹²³

IV. First Amendment Implications:

The question of whether the First Amendment to the Constitution limits FDA's regulatory power over advertising is critical to the legal status of restrictions placed upon pharmaceutical manufacturers' dissemination of off-label use information, as well as to the constitutionality of an array of rules that govern how drug companies present their products to doctors and consumers. The Washington Legal Foundation, a free-market, conservative advocacy group funded by drug makers and other manufacturers, took charge of free-speech litigation in the 1990s with a series of D.C. federal court cases that altered the framework for regulation.

The original case, *Washington Legal Foundation v. Friedman (WLF I)*,¹²⁴ arose before passage of the FDAMA and involved WLF's claim that the 1996 FDA guidance limiting dissemination of off-label use materials unconstitutionality infringed the First Amendment rights of both manufacturers and physicians.¹²⁵

The D.C. District Court borrowed the concept of advertising as "partially protected commercial speech" from the U.S. Supreme Court's decision in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*.¹²⁶ The holding of that case was premised on the idea that while truthful advertising is valuable as a

¹²²Adams, Chris. "FDA Calls Botox Claims Misleading." *The Wall Street Journal*, Sept. 10, 2002.

¹²³*Id.*

¹²⁴*WLF I*, 13 F. Supp. 2d 51 (D.D.C. 1998).

¹²⁵*Supra* note 71 at 49.

¹²⁶425 U.S. 748 (1976).

means of conveying useful information about products, commercial speech engaged in for profit is “presumed to be more durable” than non-commercial speech.¹²⁷ Having found that off-label use thus constituted commercial speech deserving of some degree of First Amendment protection, the D.C. District Court in *WLF I* applied the four-prong balancing test from the Supreme Court’s decision in *Central Hudson*¹²⁸ to determine whether the restrictions on commercial speech for the purpose of ensuring the safety and efficacy of drugs exceeded constitutional boundaries. Under the *Central Hudson* test, a regulation of commercial speech is constitutionally permissible if “the speech in question concerns lawful activity and is not misleading, the regulation serves a substantial governmental interest, and the regulation directly advances the governmental interest without being more extensive than is necessary to serve that interest.”¹²⁹ Judge Royce Lamberth of the D.C. District Court found that while the FDA guidance satisfied the first three prongs, the fourth prong was not met since less restrictive alternatives, such as “full, complete, and unambiguous disclosure” by the pharmaceutical company, were available to advance the FDA’s interests.¹³⁰ Thus, having concluded that the FDA policy restricted more speech than was necessary to achieve the public health objective, Judge Lamberth granted the plaintiff’s motion for summary judgment and issued an injunction to prevent the FDA from enforcing the off-label use materials guidance.¹³¹

Immediately following issuance of the injunction in *WLF I*, the FDAMA was passed, prompting the FDA to ask the court in *Washington Legal Foundation v. Friedman (WLF II)*¹³² to confine the application of the injunction to the FDA guidance document. Judge Lamberth denied the FDA’s motion, however, and held the injunction to apply to Section 401 of the FDAMA. The court in *WLF II* also requested supplemental briefing on the constitutionality of the FDAMA provisions addressing off-label use, later held unconstitu-

¹²⁷*Supra* note 2 at 1333.

¹²⁸*Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557 (1980).

¹²⁹164 A.L.R. Fed. 1 (2000). “Protection of Commercial Speech Under the First Amendment: § 21: Drugs.”

¹³⁰Ascroft, Richard C. “The Impact of the Washington Legal Foundation Cases on Pharmaceutical Manufacturer Practices in the United States.” 34 INLR 95, 104 (2000).

¹³¹*Supra* note 71 at 50.

¹³²*WLF II*, 36 F. Supp. 2d 16 (D.D.C. 1999).

tional in *Washington Legal Foundation v. Henney* (*WLF III*).¹³³ The FDA appealed this decision with respect to the FDAMA provisions (although not the underlying guidance document), leading to the D.C. Circuit Court decision in *WLF IV*.¹³⁴ The court did not reach the constitutional merits of the issue in *WLF IV*, choosing instead to dismiss the government’s appeal and vacate part of the district court’s injunction to the extent it declared the FDAMA unconstitutional. The Circuit Court’s reasoning followed from the FDA’s concession in briefs and oral arguments that the FDAMA did not authorize the FDA to restrict speech. The FDA asserted that the “FDAMA established nothing more than a ‘safe harbor’ ensuring that certain forms of conduct would not be used against manufacturers in misbranding and ‘intended use’ enforcement actions.”¹³⁵ The FDA further maintained that it could use dissemination of off-label use information as evidence in enforcement actions if the manufacturer did not comply with the FDAMA safe harbor, even though such dissemination would not be considered per se illegal since no independent enforcement authority could be derived from the FDAMA provisions on off-label use.¹³⁶ Thus, *WLF IV* left the state of the law unclear; despite the adverse rulings and constitutional significance of the earlier *WLF* First Amendment holdings protecting off-label use materials as commercial speech, the FDA retained the ability to regulate off-label use materials on a case-by-case basis.¹³⁷ Moreover, *WLF IV* left open the issue of whether enforcement actions by the FDA using provisions of the FDAMA other than Section 401 to limit the dissemination of off-label use information could be challenged as unconstitutional by pharmaceutical manufacturers.¹³⁸

Beyond the context of off-label use materials, the U.S. Supreme Court recently adjudicated the constitutionality of restrictions on commercial speech concerning the promotion and advertising of compounded drugs in *Thompson v. Western States Medical Center*.¹³⁹ “Drug compounding” is a process by which a

¹³³ *WLF III*, 56 F. Supp. 2d 81 (D.D.C. 1999).

¹³⁴ *WLF IV*, 202 F.3d. 331 (D.C. Cir. 2000).

¹³⁵ *Supra* note 71 at 51.

¹³⁶ *Id.*

¹³⁷ *Id.*

¹³⁸ *Supra* note 130 at 106.

¹³⁹ 122 S. Ct. 1497 (U.S. 2002).

pharmacist alters ingredients to tailor a medication to a patient's needs, typically when the medication is not otherwise commercially available.¹⁴⁰ The FDAMA exempts compounded drugs from the standard NDA requirements upon the condition that pharmacies abide by certain restrictions, such as the requirement that prescriptions for compounded drugs be "unsolicited" and that compounders not advertise or promote their products.¹⁴¹ Pharmaceutical companies brought suit in *Thompson*¹⁴² to enjoin enforcement of these restrictions on the grounds that the limitations on advertising and promotion were broader than necessary to promote the alleged governmental interests in protecting public health and safety, ensuring the integrity of the drug approval process, and preserving the availability of compounded drugs for patients with particularized medical needs. The Ninth Circuit agreed with the pharmacies, as did the Supreme Court, in an opinion written by Justice O'Connor. The government attempted to draw a distinction between small-scale and large-scale drug compounding by recognizing the economic infeasibility of safety and efficacy testing for the former. Nonetheless, O'Connor held that less restrictive means were available aside from speech-related restrictions, pointing out that the government "might ban the use of commercial-scale manufacturing in the production of compounded drugs or prohibit pharmacies from offering compounded drugs at wholesale to other licensed persons or commercial entities for retail."¹⁴³ O'Connor also noted the beneficial aspects of speech that would be lost with the FDAMA restrictions still in force, as demonstrated by the example of a pharmacist that would be prevented from informing physicians about the availability of alternative drugs through compounding, even when that pharmacist had no interest in mass-producing compounded drugs.¹⁴⁴ "If the First Amendment means anything, it means that regulating speech must be a last – not first – resort," O'Connor wrote. "Yet here it seems to have been the first strategy the Government thought to try."¹⁴⁵

¹⁴⁰*Id.* at 1500. For example, patients may have an allergy to an ingredient in a mass-produced product or children may need diluted doses of a medication.

¹⁴¹*Supra* note 129.

¹⁴²*Supra* note 139.

¹⁴³*Id.* at 1506.

¹⁴⁴*Id.* at 1509.

¹⁴⁵*Id.* at 1507.

The outcome in *Thompson*¹⁴⁶ could be seen as predictable in light of an earlier holding by the federal appeals court in *Pearson v. Shalala*,¹⁴⁷ where the court dealt with labeling claims by a dietary supplement manufacturer as opposed to a maker of prescription drugs. The 1990 Nutrition Labeling and Education Act (NLEA) liberalized the FDCA and created a statutory “safe harbor” for dietary supplements and foods that make health claims so as to enable them to avoid designation as a “drug” and thereby escape the more extensive approval and labeling requirements for drugs.¹⁴⁸ Nonetheless, *Pearson*¹⁴⁹ holds First Amendment doctrinal significance here in the context of commercial speech, as the Court of Appeals opted for the least restrictive means of curing misleading advertisements and directed the FDA on remand to determine whether a disclaimer could be added to the claim that folic acid reduces the risk of spinal cord defects, rather than permitting the FDA to ban the claim altogether. Plaintiff supplement manufacturers followed up this decision in 2001¹⁵⁰ by moving for a preliminary injunction challenging the FDA’s application of the legal standard articulated by the Court of Appeals in 1999. The District Court for the District of Columbia held a preliminary injunction warranted on the grounds that plaintiffs demonstrated a likelihood of success on the merits that the FDA’s continued refusal to authorize the folic acid health claims, even with disclaimers, violated the First Amendment.¹⁵¹

In an effort to bring FDA regulations into line with the constitutional trend of these court decisions protecting commercial speech, FDA general counsel Troy initiated a policy review by seeking public comment during the period from May through September of 2002.¹⁵² Prior to joining the Bush administration, Troy worked on

¹⁴⁶*Supra* note 139.

¹⁴⁷164 F.3d 650 (D.C. Cir. 1999).

¹⁴⁸*Pearson v. Shalala*, 130 F.Supp.2d 105, 107-8 (2001).

¹⁴⁹*Supra* note 147.

¹⁵⁰*Supra* note 148.

¹⁵¹*Id.* at 112.

¹⁵²Editorial. “Free Speech and the FDA.” *The Wall Street Journal*, Sept. 20, 2002.

the side of the Washington Legal Foundation in the late 1990s to sue the FDA over promotion and marketing issues, and advocated for drug and tobacco companies to challenge agency efforts to restrict advertising, so that the First Amendment has become his “signature issue.”¹⁵³ Conservative judges, academics, and advocacy groups are leading the push towards a “rules retreat,” however congressional Democrats and consumer groups strongly oppose any relaxation of the rules they consider to be “vital to the public health.”¹⁵⁴ The former network supports the notion that FDA’s pre-emptive speech rules are overly paternalistic, “based on false assumptions that the masses are ignorant and today’s pharmaceutical makers are no better than old time snake oil salesman.”¹⁵⁵ Republican House Energy and Commerce Committee Chairman Tauzin of Louisiana commented, “I think if a product is legal, we ought to be able to talk about it publicly without government restricting our conversation.”¹⁵⁶ Drugmakers, as well as the National Venture Capital Association, argued that the FDA’s current policy applies a “double standard” to the dissemination of off-label information in so much as “an independent researcher can freely hand out such a reprint, while the maker of the drug can’t.”¹⁵⁷ In addition to relaxing the rules governing off-label use promotion, the pharmaceutical industry wants to eliminate the FDA requirement that manufacturers prominently place the generic name for a drug alongside its brand name in advertisements, as well as the requirement that drug makers list all possible side effects in print magazine ads.¹⁵⁸

On the other side of the debate, California Democrat Representative Henry Waxman, along with eight other Democrats, warned in a letter to the FDA that “Americans could lose their lives” if the agency rules were loosened.¹⁵⁹ Waxman stated, “The First Amendment shouldn’t force us to return to a time the public health

¹⁵³*Supra* note 56.

¹⁵⁴Adams, Chris. “Looser Lips for Food and Drug Companies? Industries Pressure FDA to Relax Rules on Commercial Speech.” *The Wall Street Journal*, Sept. 17, 2002.

¹⁵⁵*Supra* note 152.

¹⁵⁶*Supra* note 154.

¹⁵⁷*Id.*

¹⁵⁸*Id.*

¹⁵⁹*Id.*

would be endangered – where manufacturers can profit by giving misinformation or deceptive information, and where it could be years before any product could be taken off the market.”¹⁶⁰ William B. Schultz and Michael R. Taylor, former deputy commissioners for policy at the FDA (serving from 1994-1998 and 1991-1994 respectively), wrote an editorial for *The Washington Post* critiquing the behavior of government lawyers in calling into question the “common-sense assumptions” of the American public – that drug companies should be required to demonstrate the safety and effectiveness of their products before they are promoted.¹⁶¹ In responding to the notion that the First Amendment severely limits the government’s role in monitoring commercial speech about drugs and other products with serious health consequences, Schultz and Taylor wrote, “It is hard to imagine that this was the intent of the Founders in 1789 or is in the public’s interest today.”¹⁶² Yet, an editorial appearing in the *Washington Post* in June 2002 presented the counterargument that, “If anything places ‘public health protections in jeopardy,’ it is the FDA’s past refusal to consider potential constitutional limitations on its authority. By seeking public comment on existing programs, the FDA will be able to ensure that its policies and regulations comply with constitutional requirements and survive the inevitable legal challenges.”¹⁶³

The policy balance surrounding free speech arguments for prescription drug information involves a re-emergence of the underlying tension between personal freedom and scientific rationality. Critics of off-label marketing lean toward the latter value preference as they view the limited regulation of commercial speech as “more than justified” by the anticipated savings in health and lives.¹⁶⁴ As the academic Dr. Arnold S.

¹⁶⁰*Id.*

¹⁶¹Schultz, William B. and Taylor, Michael R. Editorial: “Hazardous Hucksters: When it comes to public health, some limits on advertising are necessary.” *The Washington Post*, May 28, 2002.

¹⁶²*Id.*

¹⁶³Adler, Jonathan H. Editorial: “About Time at the FDA.” *The Washington Post*, June 9, 2002.

¹⁶⁴*Supra* note 64 at 211.

Relman observed, “either credible evidence of the safety and effectiveness for unapproved uses of the drug is lacking, or else the manufacturers simply have not bothered to present existing data to the FDA.”¹⁶⁵ In either case, Relman continued, it is “reasonable” for the public to be “skeptical about such uses of prescription drugs.”¹⁶⁶ Free speech proponents, though, favoring the value of personal freedom, would reply to an argument like Relman’s that “quackery is best countered by challenge and debate rather than by stifling the flow of information.”¹⁶⁷ Thus, the question comes down to the meaning attributed to “social cost” and the angle from which the FDA regulation is perceived, whether in terms of restricting the free flow of information and hindering medical innovation or protecting the public health and safety and ensuring the dissemination of reliable data.

Inequity for the Internet?

The FDA has not issued draft or final guidance regulations that specifically pertain to the Internet, leaving manufacturers room to interpret the general guidelines in ways that may be contrary to the public interest, but also opening up the possibility of agency scrutiny in every case the Internet is used for prescription drug advertising since Internet materials do not fit under the FDAMA “safe harbor.”¹⁶⁸ In this way, the Internet functionally enjoys less First Amendment protection than traditional, paper-based materials.¹⁶⁹

The World Wide Web allows for creation of “home pages” or “Web sites” which can link to other sites as well as chat rooms where live discussions on a product can take place.¹⁷⁰ The difficulty with too *little* regulation occurs when a manufacturer “hyperlinks” to the homepages of electronic journals that describe

¹⁶⁵ *Id.*

¹⁶⁶ *Id.*

¹⁶⁷ *Id.* at 210.

¹⁶⁸ *Supra* note 71 at 55.

¹⁶⁹ *Id.*

¹⁷⁰ Reichertz, Peter S. “Legal Issues Concerning the Promotion of Pharmaceutical Products on the Internet to Consumers.” 51 Food and Drug L.J. 355, 359 (1996).

off-label uses for the manufacturer's drug product, rather than directly linking to the page that contains a description of the unapproved use, in an effort to avoid an enforcement action for misbranding. This process is described as the "two-click rule" because two separate clicks of the mouse are required to reach the off-label use materials.¹⁷¹ Failure to enjoin manufacturers from engaging in this practice has created an unwritten rule of behavior that threatens public health and safety in so much as the links connect to sites that may be extremely biased or without scientific merit. The FDA will likely only have authority to regulate links from regulated companies, as opposed to being able to monitor the Web page of a publication such as the Journal of the American Medical Association (JAMA).¹⁷² However, links to JAMA do not present as much of a concern for the FDA as do sites that only discuss the off-label uses of a drug product.

The difficulty with too *much* regulation, however, lies in the danger of stifling the unique potential of the Internet and inhibiting free speech if the FDA were to mandate strict compliance with the requirements that already exist for paper documents. The FDA needs to separately address the role of the Internet in all relevant regulations and guidances, taking into account currently unresolved issues, such as how a home page is to be submitted for purposes of obtaining FDA approval, whether that page must be submitted any time an update is made, and whether interactive and communicative features of a home page must also be disclosed.¹⁷³ The international nature of the Internet also raises the question of whether, for example, a home page – set up in Europe but available in the US – for a multinational company that advertises a drug approved only in Europe, should be considered an unlawful promotion of an unapproved new drug?¹⁷⁴ To what extent can a statement (or disclaimer) saying that the product is (or is not) intended for U.S. consumers resolve this dilemma?

V. Promotion of Unapproved New Drugs:

¹⁷¹ *Supra* note 71 at 54.

¹⁷² *Supra* note 170 at 360.

¹⁷³ *Id.*

¹⁷⁴ *Id.*

As part of the standard IND testing protocol, an investigational new drug application must be submitted to the FDA whenever a pharmaceutical manufacturer wishes to proceed beyond the pre-clinical drug testing on laboratory animals to the three phases of clinical testing on humans necessary to secure new drug approval. While an unapproved new drug may be used in human subjects pursuant to the NDA process, the FDA has consistently taken the position that an IND may not lawfully be “commercialized” prior to approval.¹⁷⁵ The FDA also initially took the related position that investigational drugs were to be used solely for investigational purposes and not for patient treatment; however, this rule eventually gave way to a number of exceptions, such as “compassionate IND” licenses,¹⁷⁶ “treatment INDs,”¹⁷⁷ and a “parallel track” policy¹⁷⁸ for patients who are unable to participate in clinical trials, to permit expanded use of experimental drugs to treat serious or life-threatening illnesses for which no alternative therapies are available. The criteria common to all of these early access programs remain rules restricting commercialization of the investigational new drugs.

In May 1987, the FDA developed and issued regulations sponsored by the Office of Management and Budget and passed on June 22nd of that year, codifying the conditions under which treatment INDs can be

¹⁷⁵*Supra* note 69 at 553.

¹⁷⁶Myers, Beth E. “The Food and Drug Administration’s Experimental Drug Approval System: Is it Good for Your Health?” 28 Hous. L. Rev. 309, 315 (1991):

The “compassionate IND” is a discretionary permit allowing a patient with an untreatable terminal illness (i.e. cancer, epilepsy, AIDS, and rare “orphan” diseases) to use an unapproved drug in a particular way. However, the FDA requires detailed recordkeeping and the development of extensive protocols for using the drugs pursuant to a compassionate IND license, thereby discouraging physicians’ use of this program even when the request is approved by the FDA.

¹⁷⁷*Id.* at 316. The “treatment IND” differs from the compassionate IND in so much as the former can be more widely used, although there are still restrictions on the drugs that qualify. Generally, approval for a treatment IND for immediately life-threatening conditions comes near the end of Phase II clinical testing, while serious, but not immediately life-threatening conditions usually receive treatment IND approval during Phase III.

¹⁷⁸Shulman, Sheila R. and Brown, Jeffrey S. “The Food and Drug Administration’s Early Access and Fast-Track Approval Initiatives: How Have they Worked?” 50 Food & Drug L.J. 503, 509 (1995):

“The parallel track initiative, outlined in a Public Health Service policy statement on April 15, 1992, established an administrative mechanism to expand the availability of ‘promising investigational therapies’ beyond the parameters of the treatment IND regulations. Access to an investigational drug may be authorized as early as the end of Phase I, provided that Phase II controlled clinical trials have been approved by the FDA and patient enrollment for those trials has been initiated.”

granted.¹⁷⁹ The regulations reiterated the requirement that, “as with all clinical use of investigational drugs, informed patient consent must be obtained and the product cannot be promoted or otherwise commercialized.”¹⁸⁰ More specifically, the regulations list the conditions that: “the sale does not constitute commercial marketing of a new drug for which a marketing application has not been approved; the drug is not being commercially promoted or advertised; and the sponsor of the drug is actively pursuing marketing approval with due diligence.”¹⁸¹ Assuming the absence of any commercialization, manufacturers are given more latitude to charge for investigational drugs under the treatment IND regulations, as compared with compassionate use INDs, as long as there is “adequate enrollment in the ongoing clinical trials under the authorized IND.”¹⁸² Sponsors may bill patients on a cost-recovery basis for a drug distributed under a treatment IND, although the amount charged may not exceed the manufacturing, research and development, and distribution costs.¹⁸³

The early access period, the time from IND designation to FDA marketing approval, provides early market exposure for a drug product, and in many cases, the opportunity to develop a positive reputation within the patient community.¹⁸⁴ However, drug companies have also viewed early access to unapproved drugs as a diversion from getting new products to the market. Pharmaceutical manufacturers fear that the results of having patients take medications in a less-controlled setting than a clinical trial might hurt manufacturers’ chance for approval of the new drug, as well as detract from participation in the clinical trials under the

¹⁷⁹H.R. Rep. No. 1092, 100th Cong., 2d Sess. 28 (1998): “Criteria for the treatment IND are that (1) there is no satisfactory alternative treatment for the disease, (2) the drug is under investigation in clinical trials under an FDA-approved IND, and (3) the sponsor of the clinical trial is actively seeking approval from the FDA for marketing the new drug. Scientific evidence must provide a reasonable basis for concluding (1) that the drug may be effective and (2) that it would not expose the patient to significant risk of additional illness or injury.”

¹⁸⁰Flieger, Ken. “FDA Finds New Ways to Speed Treatments to Patients.” FDA Consumer special report. Jan. 1995. Available at: <http://www.fda.gov/fdac/special/newdrug/speeding.html>.

¹⁸¹*Supra* note 69 at 555.

¹⁸²*Id.*

¹⁸³*Supra* note 178 at 505.

¹⁸⁴*Id.* at 506.

authorized IND.¹⁸⁵ Patient activism, though, has led the push to encourage drug companies to distribute more experimental drugs to seriously ill patients and drug companies are realizing that doing so can be an effective way to market their product before FDA approval.¹⁸⁶

The legal problem arises when pharmaceutical manufacturers *commercially* promote and market new drugs prior to FDA approval, thereby granting wider access to the drugs without even following the safeguards that apply to expanded access criteria. As part of the computer-assisted analysis of false and/or misleading drug promotions by prescription drugmakers between January 1997 through November 2002, *Consumer Reports* magazine documented sixty-two citations for the promotion of unapproved medications.¹⁸⁷ To demonstrate the problem and enforcement response, the FDA website displays an example of a request for a court-ordered preliminary injunction preceded by a warning letter sent to Lane Labs-USA, Inc., the maker of three unapproved products promoted and sold in 1999, including BeneFin (produced from shark cartilage as a treatment for cancer and other diseases), SkinAnswer (treatment for skin cancer), and MGN-3 (a rice-bran extract treatment for cancer and HIV).¹⁸⁸ Similarly, the FDA Office of Regulatory Affairs “Enforcement Story” lists examples of warnings issued for unlawful promotion of unapproved drugs, such as the marketing of a drug for relief of chronic skin disorders by Skintech 2000, Inc. without an approved NDA; likewise, a permanent injunction was obtained against Health World International, Inc. on December 1, 2000, prohibiting them from promoting or advertising their drug products as “safe and/or effective in the cure, mitigation, treatment or prevention of any disease, unless and until an approved new drug application authorizing such representation is in effect for such drug product.”¹⁸⁹

The question of whether a marketing restriction should apply to control access to unapproved new drugs as a policy matter might appear less clear cut when evaluated in light of the anecdotal stories told by patients and

¹⁸⁵Fuhrmans, Vanessa. “How to Get New but Unapproved Drugs.” *The Wall Street Journal*, Dec. 5, 2002.

¹⁸⁶*Id.*

¹⁸⁷*Supra* note 22 at 35.

¹⁸⁸“FDA Takes Action Against Firm Marketing Unapproved Drugs.” Dec. 10, 1999. *Available at:* <http://www.fda.gov>.

¹⁸⁹See “The Enforcement Story,” *available at:* http://www.fda.gov/ora/about/enf_story/ch3/cder4.htm.

their family members. For example, the husband and two teenage sons of Ruth-Ann Santino, a 51-year-old woman who died from colon cancer in 2001, are still fighting to improve access to experimental drugs for terminal cancer patients.¹⁹⁰ Neither the government nor a hospital can force a pharmaceutical company to hold trials and grant expanded-access to experimental medications for selected patients test subjects who meet specific medical criteria and have exhausted all alternative treatment options. However, increasing public information about clinical trials and encouraging drug companies to open these trials to more patients are significant changes that agencies like the National Cancer Institute are helping to implement.¹⁹¹ A lawsuit was recently filed against Intermune, Inc. by Joseph Stendig, age seventy-five, who was diagnosed two years ago with a lung disorder known as idiopathic pulmonary fibrosis (IPF), from which patients die an average of three years after diagnosis.¹⁹² Stendig charged Intermune with unfair business practices, alleging that the pharmaceutical manufacturer is stifling research programs on the drug pirfenidone, a potential treatment for IPF, in order to prolong the hold of a competitor drug on the market and to avoid the difficulty of signing up clinical trial subjects for the NDA process.¹⁹³ Intermune's executive vice president of medical and scientific affairs disputes this allegation, claiming that the "company has actually accelerated the schedule for clinical development of the drug."¹⁹⁴ According to Paul Lombardo, a former California health care attorney and current University of Virginia professor of research regulations, Stendig's suit might not go forward anyway for lack of standing. "To win, he'd have to prove his claim that his health is declining because he can't get pirfenidone. To do that, he'd have to prove that the experimental drug works. That may only be possible if Intermune can complete controlled clinical trials."¹⁹⁵

¹⁹⁰Noonan, Erica. "Hope from Heartbreak Family Fights on for Better Access to Experimental Drugs." *The Boston Globe*, Mar. 24, 2002.

¹⁹¹*Id.*

¹⁹²Tansey, Bernadette. "The dilemma of a dying man; Patient sues to get unproven drug that may help defeat disease that is slowly strangling him." *The San Francisco Chronicle*, Feb. 16, 2003.

¹⁹³*Id.*

¹⁹⁴*Id.*

¹⁹⁵*Id.*

The benefits of speeding seriously ill patients' access to potentially life-saving drugs and avoiding the costs of time and expense associated with the lengthy NDA process must be offset against the safety and effectiveness concerns that underlie the drug approval process in the first place. Critiques of treatment INDs surface from citizen advocacy groups, the Pharmaceutical Manufacturers Association, the FDA, and seriously ill patients alike, albeit for different reasons: the concern that treatment INDs "clearly circumvent the legal requirement that a drug be proven effective before marketing," the fear that granting treatment INDs will "draw potential subjects away from the clinical trials necessary for full FDA approval," the complaint that treatment INDs have "such narrowly defined criteria that only a small number of patients can actually qualify to receive the drug," and the criticism that treatment INDs are "only available to wealthy, well-connected patients" since the treatments are not covered by private health insurance or Medicaid and must be carefully supervised by a physician.¹⁹⁶ The danger of commercializing as yet unproven drugs ties into the need for scientific rationality. A company may promote a drug simply to attract investors to fund further development, even when the drug is not suitable for use, either because at best, the drug has no therapeutic value, or at worst, the drug has serious or fatal side-effects. With insufficient details known about potential side effects and effectiveness, bringing new drugs to the market attaches a risk-benefit calculation to speeding the "journey from laboratory to bedside" for devastating illnesses.¹⁹⁷ What makes this analysis so difficult is that the goal of protecting public health and safety can be logically situated on either side of the line between permitting and prohibiting access.

VI. Recommendations:

¹⁹⁶*Supra* note 176 at 317-18.

¹⁹⁷*Supra* note 180.

The FDA's enforcement tools, as conferred by the FDCA, include injunctive relief, criminal penalties, and seizure powers. This section will consider other suggested measures to curb false and misleading advertisements, promotion of unapproved uses of approved drugs, and commercialization of still-experimental drugs. While the inherent push-pull tension between scientific rationality and personal freedom can't ever be fully reconciled, action can be taken to mitigate the pervasive fraud and consequent adverse public health and economic effects that surface from a relaxation of the rules governing pharmaceutical manufacturers' promotional practices.

The FDA currently lacks the authority to levy civil monetary penalties for violative conduct pertaining to the marketing of prescription drugs, despite having been given the authority to levy fines of up to \$1,000,000 per proceeding on device manufacturers and involved individuals under the Safe Medical Devices Act of 1990.¹⁹⁸ In discussing its ability to regulate prescription drug promotions at a 1994 congressional hearing, the FDA testified that, "The main issue here is not science ...or taking care of patients; the main issue here is money and how to get more of it. And ...when you're trying to basically fight economic crimes, you have to be able to fight money with money."¹⁹⁹ Politicians are responding to the FDA's assertion with various legislative proposals, such as giving the FDA the authority to levy up to \$10 million in fines for false or misleading drug advertising, limiting the federal tax deductions drugmakers can take for advertising to the amount they take for research and development, requiring disclosure of ad revenues and eliminating tax deductions for advertising altogether, urging the federal government to adopt stricter standards, etc.²⁰⁰

Recommendations for enhancing FDA enforcement also include amending or supplementing current FDA regulations with more stringent requirements when prescription drugs are advertised directly to consumers.

¹⁹⁸ *Supra* note 42 at 59.

¹⁹⁹ *Id.*

²⁰⁰ *Supra* note 22.

President of the National Consumers League, Linda Golodner, suggests that the government should require “easier-to-understand” side effect information on ads, which often appear in “virtually unreadable, jargon-filled fine print.”²⁰¹ Use of “patient-friendly language” in addition to a standard percentile over which all adverse reactions are reported, may be a way to cut down on the complete list of side effects while providing a uniform number with which patients can accurately make comparison judgments between related medications.²⁰² In assessing how DTC ads can best contribute to a more informed consumer, the question arises as to whether an exception to the learned intermediary doctrine should be carved out for these ads, thereby imposing a legally recognized duty upon manufacturers to directly warn consumers about potential risks.²⁰³ In addition to the difficulty of manufacturers conveying an adequate warning to the consumer (since a physician’s decision to prescribe a certain treatment is based on a complex set of factors relating to the patient’s individual characteristics and preferences, clinical diagnosis and treatment options), however, there would likely be a “chilling effect” on the use of DTC ads that results from potential liability. Such a dramatic cutback would, in turn, deprive consumers of the benefits discussed earlier under Part II of this paper, such as calling attention to under-treated disorders and improving patient compliance with medical treatments.²⁰⁴ Perhaps a better approach to curbing false and/or misleading drug advertisements would be to strengthen FDA enforcement by increasing efficiency. In response to the HSS policy requiring legal review of all regulatory letters before they are sent to prescription drugmakers, either the FDA should design a method to speed up its review process or Congress should authorize funds for more reviewers to screen drug ads to ensure prompt withdrawal of misleading ads before they run their broadcast cycle.²⁰⁵

²⁰¹*Supra* note 32.

²⁰²Holtz, William E. “Consumer-Directed Prescription Drug Advertising: Effects on Public Health.” 13 J.L. & Health 199, 216 (1999).

²⁰³Allen, Michael C. “Medicine Goes Madison Avenue: An Evaluation of the Effect of Direct-to-Consumer Pharmaceutical Advertising on the Learned Intermediary Doctrine.” 20 Campbell L. Rev. 113, 129 (1997).

²⁰⁴*Id.*

²⁰⁵*Supra* note 22 at 37.

Improving regulation of DTC ads to increase consumer protection may also be a means of controlling soaring prescription drug prices, going back to the problem of costly new drugs being promoted to replace older drugs at the time the patent expires without proportionately improving benefits. The Oregon Health Plan adopted a two-step procedure in 2001 to replace expensive brand-name drugs with substitutes that are as effective but cheaper: First, “discover and list which drugs offer the greatest benefits at the lowest costs. Then train doctors to prescribe drugs from this so-called formulary in most cases.”²⁰⁶ Having panels of experts check new drugs against others used for the same illnesses is intended to keep “off-the-mark prescriptions, excessive utilization and overdoses, adverse reactions, and therapeutic failures” to a minimum while reigning in costs.²⁰⁷ Similarly, the *Consumer Reports* study concluded that Congress should enact legislation to promote independent analysis of the relative cost and efficacy of competing medications to give doctors and consumers a source of reliable, unbiased information.

As part of exploring alternative strategies for enforcement, it is important to recognize that protective mechanisms exist to control pharmaceutical manufacturers’ dissemination of off-label uses for approved drugs outside of regulatory restrictions on commercial speech. Product liability law and the failure to warn arises under the “learned intermediary doctrine” when pharmaceutical manufacturers do not provide “reasonable instructions or warnings regarding foreseeable risks of harm” to the prescribing physician.²⁰⁸ Thus, manufacturers might resist disseminating off-label information in order to be able to invoke the defense of FDA approval which bars punitive damages in four states (Arizona, Ohio, Oregon, and Utah) and is at least one factor considered by other jurisdictions.²⁰⁹ Whether the “FDA Defense” should act as a complete bar

²⁰⁶ *Supra* note 26.

²⁰⁷ *Id.*

²⁰⁸ *Supra* note 130 at 108.

²⁰⁹ *Id.* at 109.

to product liability actions remains uncertain, though a law like the 1995 product liability bill passed by the House of Representatives²¹⁰ would arguably provide companies with an additional incentive to conduct the studies needed to obtain FDA approval of off-label indications for the drugs. Another means to affect companies' incentive structure would be a recommendation that the FDA give priority review to NDAs submitted in conjunction with manufacturers' applications to promote off-label uses for already-approved drug products.²¹¹ This process would protect the FDA's safety and effectiveness mandate as well as increase the marketability of drugs for manufacturers that have received the FDA seal of approval.

The Lanham Act, which provides for a cause of action for unfair competition resulting from false advertising, is another means to protect consumers from manufacturers' misrepresentations about their own as well as competitor's products with respect to the dissemination of off-label information. False scientific establishment claims most often form the basis of Lanham Act cases associated with pharmaceutical products, usually including fact patterns relating to "no 'real' science, distortion of science, old science that is no longer relevant, unreliable science, and/or good science, but the data does not support the statement."²¹² However, as the dissemination of scientific data published in a peer-reviewed journal isn't necessarily "false and misleading" just because it doesn't meet the evidentiary standard of "substantial evidence" required for FDA-approval of the use, the Lanham Act is not always as far-reaching as the marketing violation under the FDCA.²¹³

The need for manufacturers to retain credibility and build a positive reputation in the competitive pharmaceutical marketplace should itself, in theory, play a role in discouraging manufacturers' provision of off-label information about their product. However, as discussed earlier, the inability of consumers to assess the

²¹⁰*Id.* at 116. The 1995 product liability bill, although not enacted into law, contained an FDA Defense provision that stated punitive damages would not be awarded against a manufacturer "if the product involved was subject to pre-market approval by the FDA . . . and such drug was approved by the FDA." Punitive damages would also be barred "if the drug is generally recognized as safe and effective pursuant to conditions established by the FDA and applicable regulations, including packaging and labeling."

²¹¹*Supra* note 67 at 663-4.

²¹²*Supra* note 130 at 113.

²¹³*Id.* at 117.

qualities of the drug product without first using the product, thereby subjecting themselves to the possibility of direct adverse side effects or indirect health effects from the failure to use alternative medication, prevents manufacturers' economic self-interest from correcting the market failure of asymmetric information. Yet, the argument can be made that since the FDAMA limits the relaxation of off-label marketing rules to specific enumerated groups that include physicians and other qualified health care professionals, the flow of information is restricted enough that manufacturers can monitor themselves as long as there is full disclosure to physicians and patients.²¹⁴ As discussed under Part III of this paper, the FDAMA provisions that cover disclosure requirements to physicians, such as identifying sources of funding for the research cited and disclosing any conflicts of interests, are intended to compel pharmaceutical manufacturers to provide a more balanced, complete picture of their off-label marketing practices so that medical professionals gain an unbiased understanding of the benefits and risks of the off-label use. Providing full disclosure to patients by requiring doctors to tell their patients that the off-label treatments have not been approved by the FDA, to explain the known risks and benefits, and then to permit the patients to decide whether to undertake a certain treatment, ultimately shifts the decision-making responsibility onto the patients. This approach leans toward the personal freedom policy viewpoint, preserving commercial speech rights and framing the issue as one of "empowerment" for patients, while subjugating patient safety concerns to the notion of medical progress.²¹⁵

Conclusion:

The competing good values of scientific rationality versus personal freedom, often expressed in terms of

²¹⁴*Supra* note 64 at 221.

²¹⁵*Id.* at 224.

safety and effectiveness versus medical innovation, reliable and objective information dissemination versus unrestrained commercial speech, are not necessarily mutually exclusive in full. There is room for overlap in views as the preference holder travels further away from the extremes, perhaps best displayed by the expanded access programs that permit use of unapproved drugs for treatment purposes in limited cases. However, there is a constant, reciprocal tension underneath these policy perspectives that drives the direction of the law, best uncovered by juxtaposing changes in the structure of the law with the marketing practices of prescription drug manufacturers. The trend toward a relaxation of the rules restricting the promotional behavior of the pharmaceutical industry – with the expansion of advertising mediums, slower FDA response time to misleading DTC advertisements, FDAMA provisions liberating the dissemination of off-label information to physicians, and recent First Amendment court decisions embracing protected commercial speech – reveals the contemporary triumph of the personal freedom approach... and the accompanying marketplace of frauds. With the statutory aim of protecting the public health and safety, the FDA must decide how best to modify its enforcement strategy so as to re-align the policy balance to meet drugmakers promotional violations and the public's economic and health related expectations, while preserving incentives for medical progress and upholding the constitutional principles of free speech.